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Time to abandon microalbuminuria?

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The term microalbuminuria – a urinary albumin excretion (UAE) between 20 and 200 μg/min – has been introduced to identify subjects at increased risk of renal and cardiovascular disease. However, the relationship between albuminuria and risk is not restricted to the microalbuminuric range and extends to as low as 2–5 μg/min. On the contrary, the increase of UAE above 200 μg/min (macroalbuminuria) heralds the onset of proteinuria (urinary protein excretion above 0.5 g/24 h) and progressive renal and cardiovascular disease. Albuminuria is a component of the metabolic syndrome and may represent a marker of the increased risk of renal and cardiovascular disease associated with insulin resistance and endothelial dysfunction. Proteinuria is a sign of established kidney damage and plays a direct pathogenic role in the progression of renal and cardiovascular disease. Albuminuria reflects functional and potentially reversible abnormalities initiated by glomerular hyperfiltration, proteinuria, a size-selective dysfunction of the glomerular barrier normally associated with glomerular filtration rate (GFR) decline that may result in end-stage renal disease. Thus, the limit of 200 μg/min segregates patients with albuminuria or proteinuria who are at quite different risk. Among subjects with albuminuria, however, there is a continuous relationship between albumin excretion and risk and no lower bound between normal albuminuria and microalbuminuria can be identified that segregates subjects at different risk. Thus, the terms microalbuminuria and macroalbuminuria could be replaced by the concepts of albuminuria- and proteinuria-associated diseases. Future studies are needed to identify levels of albuminuria below which therapy is no longer beneficial.

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WHY MEASURING ALBUMINURIA?

It is now 40 years since Keen *et al.*[1] had reported an increase in urinary albumin excretion (UAE) in 'newly detected hyperglycemics'. The term microalbuminuria, however, first appeared in the medical literature in 1981, used by Viberti[2] and Svendsen,[3] to describe a UAE below the detection limit of a standard dipstick, but at a level that, as reported by Mogensen *et al.* in 1986,[4] was highly predictive of future overt nephropathy in patients with type I diabetes. Shortly thereafter, it became evident that microalbuminuria predicted mortality, largely from cardiovascular events, in patients with type II diabetes.[5] Since then, microalbuminuria – defined as a UAE between 20 and 200 μg/min or 30 and 300 mg in overnight and 24 h urine collections, respectively – has been identified as a newly recognized cardiovascular and renal risk factor in both diabetic and non-diabetic subjects.[6,7] However, although the lower bound was chosen because 95% of 'normal' individuals had excretion rates below that limit, it was recognized that risk of cardiovascular events and of progression to overt nephropathy was elevated also in subjects in the 'high normal' range.[8–10] Similar to the relationship between blood pressure and risk of cardiovascular events, mounting evidence indicates a continuous relationship between UAE and risk. And like blood pressure, the concept of a threshold level to define normality is inconsistent with epidemiological data.[11] Indeed, *post hoc* analyses of randomized trials in high-risk individuals as well as community-based cohort studies all indicate that incremental increases in albuminuria within the 'normal' range carry higher risks of nephropathy or cardiovascular events.[8–10] Data from the BErgamo NEphrologic Diabetes Complications Trial[12] showed that high normal albuminuria is the strongest predictor of the onset of microalbuminuria in patients with type II diabetes. (Perna *et al.*, personal communication). The Heart Outcome Prevention Evaluation study[8] also showed that the relationship between albuminuria and experiencing a cardiovascular event extends to as low as 0.5 mg/mmol (albumin/creatinine ratio (*A*/*C*)). On the same line are data from the Losartan Intervention For End point reduction in hypertension study[9] and several population studies,[10,13,14] In particular, the Framingham Heart Study found that 6-year risk of cardiovascular disease was threefold higher in nonhypertensive, non-diabetic subjects with urinary *A*/*C* above the gender-specific median (3.9 μg/min for men and 7.5 μg/min for women) than in those with

urinary *A/C* below the median.[13] The above evidence led Forman and Brenner[11] to suggest that 'Microalbuminuria is another term that should now be eliminated from our lexicon, as there are ample data to suggest that albuminuria in the 'normal' range carries significant risk of cardiovascular events'. A further argument in favor of this is that the term microalbuminuria is also incorrect, since it should reflect small albumin molecules, and not small amounts of albumin. This is further confusing owing to the growing evidence that, in addition to the whole molecule, 'normal' urine may contain different immunoreactive moieties and albumin fragments.[15] Thus, the concept of normal or abnormal albuminuria should be abandoned and the unifying term of albuminuria could be used to describe measurable amounts of albumin in the urine. On the other end, UAE above the limit of 200 μg/min appears to clearly identify a different subgroup of patients with progressive renal disease and a cardiovascular mortality rate that exceeds by about sixfolds the rate observed in subjects with lower levels of albuminuria or no evidence of urinary abnormalities.[16] Notably, in these patients, albuminuria is invariably associated with proteinuria and worsening renal function.[17] Renal insufficiency and overt proteinuria may cause volume overload and worsen hypertension, dislipidemia, and endothelial dysfunction, all of which may independently sustain the excess renal and cardiovascular mortality in this typology of patients.[18]

ALBUMINURIA: A CONSEQUENCE OF INSULIN RESISTANCE?

Albuminuria is often associated with the metabolic syndrome, a syndrome of insulin resistance, obesity, hypertension, dislipidemia, and increased renal and cardiovascular morbidity. Several evidences suggest that insulin resistance precedes and probably contributes to the development of microalbuminuria in type I diabetic patients,[19] as well as in non-diabetic subjects.[20] Data in type II diabetic patients, however, were less clear.[20,21] The hypothesis of an association between insulin resistance and microalbuminuria was recently revived by a cross-sectional study showing that in a large cohort of type II diabetic patients, the homeostasis model assessment index, a surrogate of insulin sensitivity, was significantly associated with the *A/C* ratio measured in spot urine collections.[22] To formally test this possibility, we compared the total-body glucose disposal rate, quantified by means of a euglycemic hyperinsulinemic clamp technique, in 50 matched pairs of type II diabetic patients with micro- or normo-albuminuria.[23] Data showed that subjects with microalbuminuria were more insulin resistant than those with a normal urinary albumin excretion, and that the magnitude of insulin resistance was independently associated with microalbuminuria. Of interest, there was a clear association between more severe insulin resistance and microalbuminuria also in the subgroup of patients with normal blood pressure considered separately from those with arterial hypertension. Altogether, these findings lend support to the possibility that insulin resistance is directly associated with albuminuria, regardless of its relationships with arterial hypertension. On the other hand, finding in a collateral study that insulin sensitivity was similar in patients with macro- or microalbuminuria and was not correlated with the degree of urinary albumin excretion confirmed that increased albuminuria is not *per se* a primary determinant of insulin resistance.

Thus, increased albuminuria could be taken as an indicator of insulin resistance and of the increased renal and cardiovascular risk (the cardio-renal syndrome) associated with the metabolic syndrome.

WHY SHOULD INSULIN RESISTANCE ENHANCE ALBUMINURIA?

The role of endothelial dysfunction

Insulin resistance has been related to endothelial dysfunction.[24,25] Endothelial cells release both relaxing and contracting factors that modulate vascular smooth muscle tone and also participate in the pathophysiology of essential hypertension.[26] Under physiological conditions, there is a balanced release of endothelial-derived relaxing and contracting factors, but this delicate balance is altered in conditions frequently associated with albuminuria such as hypertension, diabetes, obesity, thereby contributing to further progression of vascular and end-organ damage.[27] In particular, endothelial damage/dysfunction, leading to decreased bioavailability of nitric oxide, impairs endothelium-dependent vasodilation, which may contribute to increase the arterial blood pressure[26] and to accelerate micro- and macrovascular disease.[26] Moreover, damaged endothelial cells are presumably more sensitive to the injurious effects of further insults, such as elevated blood pressure, analogue to the increased susceptibility of glomeruli to higher blood pressure in diabetes mellitus, which, in turn, may further contribute to endothelial dysfunction.[28] Endothelial dysfunction has also been associated with an increased permeability of the vascular endothelial cell layer[29] to circulating macromolecules, including lipoproteins, such as light-density lipoproteins, that have been correlated to subsequent atherogenesis.[30] This has been attributed to changes in cell surface electrostatic charge.[31] We recently reported that a nitric-oxide releasing moiety, nitro-aspirine, unlike aspirin, ameliorated hypertension, albuminuria, and whole blood glucose disposal rate in hypertensive type II diabetic patients with albuminuria and insulin resistance.[32] This supports the hypothesis that defective nitric-oxide bioavailability may play a role in the pathogenesis of microvascular damage in diabetes and may be related with insulin resistance. Actually, insulin therapy may improve endothelium-dependent and endothelium-independent vasodilatation,[33] and amelioration of insulin resistance may reduce arterial blood pressure and albuminuria.[34] Other factors, however, may play a role, as intensified insulin therapy does not invariably result in improved endothelial function.[35]

The role of renal albumin handling

A defective production of heparan sulfate proteoglycans has been observed in glomeruli of diabetic rats.[36] Proteoglycans are ubiquitous extracellular proteins that serve a variety of functions throughout the organism, including the maintenance of the glomerular filtration barrier. Decreased levels of proteoglycans may result in a decreased content of negative charges and in a reduced charge-selectivity of the glomerular barrier.[36] Synthesis of proteoglycans occurs in all three glomerular cell types, in particular podocytes, and, *in vitro*, is inhibited by high ambient glucose and angiotensin II.[37,38] Thus, hyperglycemia and activation of the renin angiotensin system (RAS) might contribute to a loss of charge-dependent restriction of macromolecule filtration at the glomerulus that might facilitate albumin ultrafiltration. Alternatively, glycosylation of circulating albumin may shift its net charge toward a more neutral range. An increase in the charge microheterogeneity of serum albumin – with an increase in the isoelectric point – has been described in adolescents with diabetes.[39] Cationization of albumin changes its spatial configuration[40] and may thus also influence its size-based exclusion by the capillary wall[39] or increase its binding to the negatively charged brush border of proximal tubule cells, thereby increasing its reabsorption.[41] Finally, albumin glycosylation cannot explain enhanced albuminuria in obese or hypertensive subjects with decreased insulin sensitivity, but no overt diabetes.

Albuminuria may be the consequence of decreased albumin re-uptake at tubular level. Endocytotic uptake of albumin by proximal tubular cells in culture is regulated by phosphatidyl inositide 3-kinase,[42] an enzyme that in proximal tubule cell cultures is activated by insulin. This suggests that insulin might increase albumin endocytosis, possibly by stimulating interaction of clathrin-coated pits with the endosome compartment. The development of insulin resistance may therefore adversely effect tubular albumin uptake and lead to excretion of a larger fraction of the albumin that is filtered at the glomerulus.

The independent role of glomerular hyperfiltration

Perfusion of physiological concentrations of insulin into isolated rat kidneys induces vasodilatation and increases the glomerular filtration rate by a prostaglandin-dependent process.[43] In normal rats, acute hyperinsulinemia increases the renal plasma flow and the glomerular hydrostatic pressure gradient via a preferential dilatation of the afferent arteriole.[44] In genetically obese rats, the glomerular filtration rate (GFR) is increased and starts to decrease only with the development of overt proteinuria.[45] In humans, hyperinsulinemia is a typical component of the insulin-resistance syndrome that may affect subjects with obesity, hypertension, or type II diabetes.[46] Insulin resistance, estimated by the glucose-clamp technique, is positively correlated with glomerular filtration fraction and is associated with glomerular hyperfiltration.[47] Thus, insulin resistance and secondary hyperinsulinemia may cause glomerular hypertension and hyperfiltration, which, in turn, may enhance albumin ultrafiltration and excretion. Actually, severe obesity – a condition characterized by decreased insulin sensitivity [46] – is associated with high renal plasma flow,[48,49] increased GFR,[48,50] and enhanced urinary albumin excretion.[51,52] Analyses of dextran sieving data showed that the glomerular capillary bed of obese subjects is exposed to increased perfusion and elevated transcapillary hydraulic pressure resulting in hyperfiltration and increased albuminuria.[53] These functional abnormalities – that reflect a state of renal vasodilation involving, mainly or solely, the afferent arteriole – are particularly prominent in subjects with abdominal obesity – a condition associated with severe insulin resistance and the metabolic syndrome[52,54] – and may fully recover with weight loss.[55] Thus, the kidney of insulin-resistant subjects shears functional abnormalities with the kidney of overt diabetics and, as the diabetic kidney, is susceptible to damage and eventual development of overt proteinuria and glomerulosclerosis.[56]

Insulin resistance may also affect the GFR via its effects on systemic blood pressure. Hyperinsulinemia sustains salt- and volume-dependent hypertension by directly promoting sodium and water reabsorption at tubular level,[57] by activating the sympathetic nervous system activity,[58] and by inducing endothelial dysfunction (see above). Systemic hypertension may then contribute to glomerular hypertension and increased albumin ultrafiltration, in particular when insulin-induced pre-glomerular vasodilation facilitates the transmission of the systemic blood pressure to the glomerular capillary.[44] Concomitant endothelial dysfunction might also enhance glomerular susceptibility to the mechanical insult.[28] On the other end, a direct effect of insulin on glomerular permeability is unlikely, as physiological hyperinsulinemia does not increase albumin transcapillary escape in healthy subjects, as well as in patients with type II diabetes.[25] The increased albuminuria observed in some studies during acute hyperinsulinemia may therefore reflect increased sympathetic activity,[58] blood volume contraction,[25] or decreased tubular albumin reabsorption.[25]

Consistent with a specific role for insulin resistance in the pathogenesis of glomerular hyperfiltration and albuminuria is the evidence that amelioration of insulin reduced the GFR and UAE in subjects with type II diabetes and microalbuminuria.[34] The significant, positive correlation between changes in GFR and albuminuria did also suggest the possibility of a cause and effect relationship between amelioration of glomerular hyperfiltration and reduction of albuminuria.

Indeed, theoretical models of albumin reabsorption in the proximal tubule[59] suggest that glomerular hyperfiltration may result in increased UAE even in the absence of size/charge-selective dysfunction of the glomerular barrier or of intrinsic abnormalities of tubular albumin endocytosis. In experimental animals, ultrafiltered albumin is largely reabsorbed in the proximal tubule[41,60] via an endocytic mechanism initiated by albumin binding to surface-expressed glycoproteins megalin and cubulin that colocalize in

endocytic pits.[61,62] Should this mechanism be inhibited, up to 90% of ultrafiltered albumin would be lost in urine.[41,60] If the same relationship were to hold in humans, then abolition of tubular reabsorption alone could result in up to 300 mg/24 h of albuminuria.[17]

In addition to receptor expression and kinetics, the rate of albumin reabsorption depends also on physical processes within the tubule lumen. For cellular uptake to occur, albumin must diffuse and/or be convected radially from the bulk tubule fluid to the endocytic pits at the bases of the microvilli. Accordingly, mass transfer resistances in the open part of the lumen and in the intermicrovillar fluid potentially limit the overall rate of albumin reabsorption. Moreover, the axial flow rate may influence how rapidly the albumin concentration falls along the tubule. When the single nephron GFR increases and more fluid is ultrafiltered through the glomerular barrier, the flow rate through the tubule increases and the residence time for albumin in the tubule decreases. Thus, the available time at tubular surface to bind and reabsorb ultrafiltered albumin decreases and the overall amount of reabsorbed albumin tends to be reduced. Moreover, when the fluid rate increases, the radial gradient of albumin concentration within the tubule may also increase and lower amounts of ultrafiltered albumin may diffuse from the tubule axis to the tubule surface. This may further limit tubular albumin reabsorption and contribute to increase UAE.

Thus, the albuminuria often observed in hyperinsulinemic subjects with obesity, hypertension, or diabetes might be explained by functional – and potentially reversible – disturbances in proximal tubule albumin reabsorption initiated by glomerular hyperfiltration. This is consistent with functional studies showing no abnormalities in glomerular size-selective function in type I[63] and type II[17] diabetic subjects with microalbuminuria and with morphological studies showing that no structural abnormalities beyond glomerular hypertrophy, mild increases in mesangial volume fraction, and basement membrane thickness are detected in kidney tissue from obese Pima Indians[17] or Caucasians (A Remuzzi, personal communication) with type II diabetes and microalbuminuria.

ALBUMINURIA AND THE CARDIO-RENAL SYNDROME: IS NEPHRON UNDERDOSING THE LINK?

Albuminuria is strongly associated with the metabolic syndrome.[64] Thus, the predictive role of albuminuria might be easily explained by the well-established association between the metabolic syndrome and increased renal and cardiovascular morbidity.[64,65] According to the Steno hypothesis,[29] albuminuria might reflect a general vascular dysfunction, and leakage of albumin and other plasma macromolecules such as low-density lipoproteins into the vessel wall may lead to inflammatory responses that in turn may start the atherosclerotic process. Moreover, the increased microvascular pressures and flows observed in diabetes and hypertension may act as injurious stimuli to the endothelium (hemodynamic hypothesis), leading to impaired vasodilatory function, excess matrix protein production, capillary basement membrane thickening, and sclerosis. In the heart, this may contribute to the impaired coronary hemodynamics associated with adaptative left ventricular hypertrophy and the consequent diminution of coronary reserve, increasing diffusion distances, failure of angiogenesis to compensate, and secondary ischemic myocyte injury.[66]

An attractive hypothesis is that a reduced nephron number at birth, 'nephron underdosing', might predispose to both renal and cardiovascular disease.[67] Aberrant fetal programming by genetic factors, malnutrition, and other insults to the pregnant mother might lead to less glomeruli. This might predispose to glomerular hyperfiltration, hypertension, albuminuria, and renal disease. According to Backer hypothesis this might also predispose to the metabolic syndrome and cardiovascular events in adult life.[68] Indeed, the relation between less nephrons and hypertension has been proven.[69] Suggestive, although not definitive, evidence for a link between fetal malnutrition and albuminuria is also available.[70] Thus, reduced nephron number at birth might be the common determinant of hyperfiltration and insulin resistance. Hyperfiltration and insulin resistance may both predispose to the development of albuminuria, in particular in concomitance with other components of the metabolic syndrome such as hypertension, obesity, or diabetes that may contribute to worsen glomerular dysfunction. In a proportion of patients, albuminuria will precede the onset of clinical proteinuria and the metabolic syndrome will predict an increased risk of cardiovascular events (Figure 1). In turn, albuminuria may be sustained by the inflammatory status that accompanies macrovascular disease.[71]

Regardless of the above, screening for albuminuria may be the most effective way to early identify subjects who are at increased risk for both renal and cardiovascular events. Other approaches to detect high-risk patients at even earlier stages might include screening for hyperfiltration or decreased insulin sensitivity. Reliable markers of hyperfiltration that can be used for population screenings, however, are missing. The homeostasis model assessment index[72] may be used to identify those who are insulin resistant. However, the predictive value of this marker for cardiovascular events is, so far, not established. Dipstick for albuminuria is easy and inexpensive, and remains the most practical way to identify subjects at risk.

WHY SHOULD PROTEINURIA INITIATE PROGRESSIVE RENAL AND CARDIOVASCULAR DISEASE?

The National Health and Nutrition Examination Survey III found that the metabolic syndrome is a strong and independent risk factor for chronic kidney disease.[64] These findings extend previous evidence that the metabolic syndrome is associated with an increased risk for diabetes, cardiovascular disease, as well as increased mortality from cardiovascular disease and all causes in the general population.[65] Longitudinal studies of the time course of GFR in type

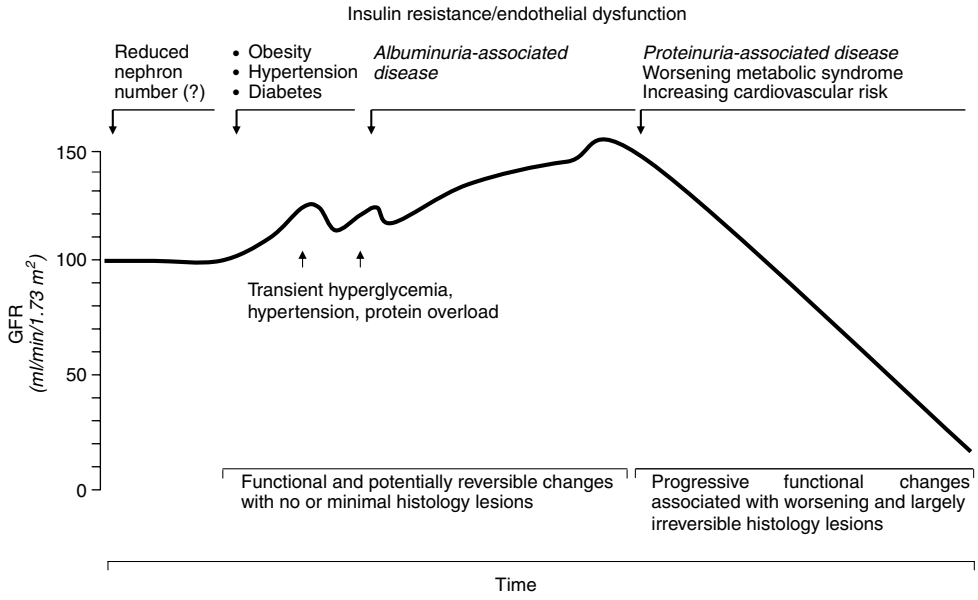

Figure 1 | Time course of albuminuria/proteinuria and GFR in a hypothetical subject at increased risk of renal or cardiovascular events because of insulin resistance and endothelial dysfunction. In a predisposed patient, possibly because of a reduced nephron number at birth, the development of insulin resistance and of the metabolic syndrome may induce and sustain a progressive increase in the GFR. Initially, this hemodynamic abnormality is fully reversible, may be transiently exacerbated by hyperglycemia, hypertension, or high protein intake, and is not associated with functional or structural abnormalities of the glomerular barrier. With time, a further increase of the GFR may *per se* sustain a progressive increase in albuminuria mediated by physical processes within the tubule that may be independent of sieving defects of the glomerular barrier. Prolonged exposure to increased intracapillary pressures, hyperglycemia, and hyperinsulinemia may progressively affect the sieving function of the glomerular barrier, which may increase albumin ultrafiltration and albuminuria. At this stage, structural abnormalities of the mesangium and of the glomerular barrier may become apparent, but glomerulosclerosis is still not evident. Without treatment, these functional and structural changes may progress and a shunt may appear that allows for the ultrafiltration of larger plasma macromolecules, including proteins other than albumin, growth factors, lipoproteins, and complement components. The enhanced traffic of these plasma components may sustain a self-perpetuating process of chronic inflammation and scarring that results in a relentless renal function loss and progression to end-stage renal disease. Diffuse glomerulosclerosis and tubulo-interstitial fibrosis become apparent. Throughout the stage of glomerular hyperfiltration and albuminuria, the cardiovascular risk may be increased because of the concomitance of the metabolic syndrome (obesity, hypertension, diabetes, dyslipidemia). With the appearance of proteinuria and renal insufficiency, renal dysfunction contributes to further enhance the cardiovascular risk to such an extent that the majority of subjects will die of cardiovascular events before progressing to end-stage renal disease. Albuminuria is therefore the marker of an excess risk associated with the metabolic syndrome and its components (albuminuria-associated disease). Proteinuria is an independent determinant of progressive renal and cardiovascular damage, which independently contributes to further increase the risk (proteinuria-associated disease).

I diabetes clearly show that, without treatment beyond blood glucose control, after several years of stable renal function, the GFR starts to decline in parallel with the appearance of macroalbuminuria.[73] Studies in the Pima Indians confirm that the GFR remains elevated until macroalbuminuria develops also in type II diabetes.[74,75] At this stage, the glomerular barrier becomes more restrictive except for the passage of large, nearly impermeant dextrans, suggesting a loss of ultrafiltration capacity and the formation of a shunt.[17,75] Thus, enhanced and unrestricted ultrafiltration of plasma macromolecules – including not only albumin but also other plasma proteins, immunoglobulins, growth factors, and complement components all of which have a specific nephrotoxicity – may initiate a self-perpetuating process of progressive glomerulosclerosis, tubulointerstitial inflammation, and scarring, with progressive renal function loss, in both diabetic and non-diabetic chronic renal disease (Figure 1).[76] Actually, altered protein traffic can exert local effects which are rather related to the nature of a given filtered protein. For example, critical amounts of transferring–iron complexes at the local acidic pH of proximal tubular fluid may release iron, which in turn promotes lipid peroxidative damage to the cytosol and cell membrane.[77] After filtration, insulin-like growth factor 1 dissociates from binding proteins and stimulates mitogenesis and synthesis of collagen I and IV in proximal tubular cells.[77,78] An additional mechanism directly relevant to inflammatory events can be mediated by a chemotactic lipid factor isolated from urine of rats with overload proteinuria.[79] A factor with identical biochemical features is released by proximal tubules exposed to fatty acid bound to albumin as a probable consequence of changes in the epithelial cell phenotype linked to the metabolism of lipoproteins.[80] Ultrafiltered complement components can also form deposits along the luminal side of proximal tubular cells in rats with protein overload nephropathy, aminonucleoside nephrosis, and remnant kidneys,[76] a pattern that is commonly observed in kidneys of patients with proteinuria and correlates with urinary

complement excretion. C3 and C5b-9 can promote tubular injury and interstitial inflammation by generating oxygen-free radicals and chemotactic gradients.[76]

Proteinuria is usually associated with extensive mesangial expansion and glomerulosclerosis, in particular in obese, type II diabetic subjects.[17,75] Mesangial expansion might impinge on the peripheral capillaries of patent glomeruli, further reducing the surface area available for filtration.[81] In addition, the thickening of the basement membrane and the widening of epithelial foot processes may reduce the hydraulic permeability of the glomerulus,[82] indicating that the decline in ultrafiltration capacity is due both to a loss of filtration area and to a reduction in glomerular hydraulic permeability.[83] The volume of the remaining open glomeruli progressively increases, perhaps as a means of compensating for the loss of filtration area and hydraulic permeability. Hyperperfusion and hyperfiltration of these remnant glomeruli may compensate for the loss of the ultrafiltration capacity. Glomerular filtration declines rapidly when the glomerular hyperperfusion can no longer compensate for the loss of ultrafiltration capacity.[74] Declining GFR and worsening proteinuria aggravate the metabolic syndrome and accelerate atherosclerosis and cardiovascular disease, which contributes to the dramatic excess cardiovascular morbidity and mortality associated with chronic kidney disease.[16,64] Altogether, these data lend support to the hypothesis that, with proteinuria, the appearance in the urine of plasma proteins different from albumin identifies the progression from functional and potentially reversible abnormalities to persistent functional and structural changes that, without treatment, sustain a relentless progression to end-stage renal disease.[75] This is consistent with evidence that, among primary chronic glomerular diseases associated with proteinuria, the only one that is normally not characterized by progressive renal function loss and irreversible kidney structural damage is 'nihil' disease, a condition normally associated with 'pure' albuminuria.[84] In those subjects with progressive renal function deterioration, urinalysis invariably shows plasma proteins also different from albumin and clearance studies disclose the appearance of a shunt allowing for an unrestricted ultrafiltration of plasma macromolecules.[84] At this stage, morphological evaluation of the kidney tissue identifies the appearance of diffuse glomerulosclerosis and tubulointerstitial infiltration, typical features of progressive nephropathies associated with proteinuria.[17,85] The pathogenic role of proteinuria is suggested by animal and human studies showing that drugs, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, that ameliorate the glomerular sieving function and reduce the shunt pathway, in addition to restrict the ultrafiltration of larger plasma macromolecules, prevent progressive kidney damage and renal function loss.[86–90]

Thus, given that substantial kidney dysfunction and structural damage are not evident before the development of proteinuria, therapeutic interventions aimed at preventing renal and cardiovascular disease might have their greatest beneficial effects in those subjects who have not yet developed macroalbuminuria.

REDUCING ALBUMINURIA: AN EFFECTIVE WAY TO PREVENT RENAL AND CARDIOVASCULAR DISEASE?

Multimodal treatment targeting urinary proteins, blood pressure, lipids, and glucose (in diabetics) may achieve remission of proteinuria and stabilization of renal function in a substantial proportion of subjects with proteinuric renal disease,[91] which may translate in a remarkable reduction in cardiovascular and all-cause mortality.[92] In about two-thirds of those with diabetes[92] and one-third of those without,[91] however, remission is not achieved and renal and cardiovascular risk remain elevated. Thus, early intervention, started before progressive glomerulosclerosis and scarring is initiated by increased protein traffic, may be important to maximize reno- and cardioprotection. In diabetes, there is no doubt that therapies that prevent or delay the development of macroalbuminuria are beneficial. The Irbesartan in Patients with type II Diabetes and Microalbuminuria showed that inhibition of the RAS by the angiotensin II receptor blocker irbesartan slowed the progression to overt nephropathy and was associated with a reduced number of cardiovascular events as compared to non-RAS inhibitor antihypertensive therapy.[93] In the BErgamo NEphrologic Diabetes Complications Trial study, RAS-inhibition by the angiotensin-converting enzyme inhibitor trandolapril, added-on optimized metabolic and blood pressure control by non-RAS inhibitor therapy, halved the risk of developing microalbuminuria in subjects with type II diabetes and arterial hypertension, but no evidence of renal disease.[12] This effect exceeded the benefit expected on the basis of blood pressure reduction alone. Notably, regardless of treatment randomization, only 13 of 1204 randomized patients died of cardiovascular disease over a median follow-up of 3.6 years. This mortality rate (0.3% per year) was 26-fold lower the rate (7.9% per year) observed – over a comparable observation period and at a comparable blood pressure control – in type II diabetic patients with macroalbuminuria included in the Reduction in Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II receptor Antagonist Losartan study.[90] Consistently, the Heart Outcome Prevention Evaluation and Losartan Intervention For End point reduction in hypertension trials[8,9] found that albuminuria reduction from baseline to losartan or ramipril treatment, respectively, predicted delayed progression to overt nephropathy and cardiovascular protection on follow-up. Finally, the Prevention of Renal and Vascular Endstage Disease Intervention Trial found less cardiovascular events in subjects with increased albuminuria on angiotensin-converting enzyme inhibitor therapy as compared to controls on non-RAS inhibitor therapy.[94] Altogether these data, indirectly, highlight the importance of early intervention, not only to prevent the onset of overt nephropathy and subsequent progression to ESRD but also to limit the excess cardiovascular morbidity and mortality associated with

proteinuria and progressive renal insufficiency, in subjects with or without diabetes.

CONCLUSION

Here we suggest that albuminuria is a marker of glomerular hyperfiltration. The frequent association of this functional and potentially reversible abnormality that is often associated with the metabolic syndrome. This likely may explain why albuminuria is also an early marker of increased renal and cardiovascular risk. Among subjects with albuminuria, any degree of measurable albuminuria bears a significant risk for renal and cardiovascular events. Data from Heart Outcome Prevention Evaluation, Losartan Intervention For End point reduction in hypertension, and Framingham studies[8,9,13] clearly suggest that only negligible amounts of albuminuria below approximately 2 mg/g of urinary creatinine (or an estimated excretion rate of 2 mg/day) should be considered as 'normal'. This approximately corresponds to a urinary concentration of 1–2 μg/ml, which is below or close to the detection limit of the methods commonly used for the measurement of urinary albumin such as nephelometry and immunoturbidimetry. Indeed, values above this threshold are significantly associated with risk for overt nephropathy, myocardial infarction, and cardiovascular death. The Heart Outcome Prevention Evaluation and Losartan Intervention For End point reduction in hypertension results further suggest that this association applies to diabetics and non-diabetics, alike.[8,9] This may have major practical implications as albuminuria can be ameliorated by amelioration of insulin sensitivity,[34] weight loss,[55] blood pressure and blood glucose reduction,[95,96] and RAS-inhibitor therapy.[8,9,12,93] In the long run, these interventions are expected to prevent or delay end-organ damage. Once proteinuria heralds the onset of overt kidney damage, a self-perpetuating process of progressive renal dysfunction and accelerated atherosclerosis is initiated that dramatically increases the overall renal and cardiovascular risk. At this stage, multimodal regimens targeted at urinary proteins, blood pressure, lipids, and blood glucose[91] may reduce the risk, but may seldom achieve full remission of kidney disease and effective prevention of cardiovascular risk, in particular in those with type II diabetes and overt nephropathy.[92] Thus, evaluating not only the amount of albuminuria but also the newly onset of proteinuria may help to better characterize the risk and to guide renal and cardioprotective therapy. To this purpose, the terms microalbuminuria and macroalbuminuria could be abandoned and replaced by the concepts of albuminuria- and proteinuria-associated diseases. Future randomized trials are needed to identify levels of albuminuria below which further therapy is no longer beneficial.

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